Best Pharmaceuticals for Children Act (BPCA)
Antipsychotic Safety Therapeutic Working Group Conference Call
May 27, 2009
10:00 p.m.–10:45 p.m. ET

Participants

Jeffrey Blumer, M.D., Ph.D., Case Western Reserve University
Judith Cope, M.D., M.P.H., Office of Pediatric Therapeutics (OPT), Food and Drug Administration (FDA)
Victor Crentsil, M.D., Center for Drug Evaluation and Research, FDA
Julie Dopheide, Pharm.D., University of Southern California School of Pharmacy
Elizabeth Durmowicz, M.D., Center for Drug Evaluation and Research, FDA
James Korelitz, Ph.D., Westat
Ron Manderscheid, Ph.D., SRA International, Inc.
Dianne Murphy, M.D., OPT, FDA
Merle Paule, Ph.D., National Center for Toxicological Research, FDA
Merrily Poth, M.D., Uniformed Services University of the Health Sciences
Adelaide Robb, M.D., Children's National Medical Center
Perdita Taylor-Zapata, M.D., NICHD, NIH
Benedetto Vitiello, M.D., National Institute of Mental Health (NIMH), NIH
Anne Zajicek, M.D., NICHD, NIH
Julie Zito, Ph.D., University of Maryland, Baltimore

Purpose

The purpose of the conference call was to discuss the following:
- Issues raised in the previous conference call
- Priority recommendations for the 2009 BPCA annual scientific prioritization meeting.

Discussion

Dr. Taylor-Zapata said that during this call or future e-mail discussions, the group should make decisions about priority recommendations that will be presented at the 2009 BPCA annual scientific prioritization meeting in November. After the call, participants will receive a survey and will vote on priority areas for study. The priority areas should be determined by July. A member of the group will need to volunteer to present the recommendations at the meeting.

Dr. Taylor-Zapata noted that during the previous call the group discussed the use of databases to determine safety signals. One limitation of using databases is that practitioners use diagnostic codes for which they will be reimbursed. However, databases can provide significant information about the cumulative effects of drugs over time. The group discussed using Medicaid, Kaiser, and Department of Defense (DOD) databases. Dr. Taylor-Zapata has contacted the DOD.

Dr. Cope said that the group should consider the generalizability of retrospective data. Medicaid data can be generalized to the population of all Medicaid children. Forty percent of children in the United States are enrolled in Medicaid and the State Children's Health Insurance Program. Databases can provide information about racial disparities in exposures. Minority children from lower socioeconomic groups are enrolled for shorter periods and have shorter exposures than continuously enrolled white children. Large data sets can also provide information about low-frequency adverse events (AEs), especially those that result from long-term exposure.

Dr. Manderscheid said that the National Comorbidity Survey would be the first survey to use research diagnostic criteria for teenagers. The database would be much more standardized than other databases and would allow correlations between diagnoses and antipsychotic drugs. The National Comorbidity Survey is sponsored by NIMH with co-funding from the Substance Abuse and Mental Health Services Administration. Ronald Kessler, Ph.D., is the principal investigator for the survey, and he has not released adolescent data yet.

Dr. Manderscheid added that he is working on a committee involved in Healthy People 2020. The committee recently completed a report on disparity and equity as a major focus of Healthy People 2020. He will send the report to the group. Dr. Poth noted that some metabolic complications are more common in African Americans. Dr. Manderscheid agreed and said that Healthy People 2020 would consider racial differences.

Dr. Poth said that there is a dearth of information about how endocrine effects mediate the effects of antipsychotic drugs. An Israeli study found higher rates of complications in children than in adults. Dr. Robb said that Christoph Correll, M.D., and Harold Carlson, M.D., have written extensively about endocrine effects. Dr. Poth asked how these researchers' data sources related to the broader population and long-term outcomes. Dr. Robb said FDA filings include 6 months of safety data. Some filings include 12 months of safety data, such as the study of Abilify for the treatment of irritability in autism. Prospective studies capture prolactin levels, insulin levels, and blood glucose. However, there are no naturalistic studies similar to the Attention-Deficit Hyperactivity Disorder Observational Research in Europe project. There are very large studies with 1–2 years of follow-up for efficacy and safety outcomes. Most of these studies are industry sponsored rather than government sponsored because they are expensive. Dr. Robb said she would send review articles on endocrine effects of antipsychotics to the group.

Dr. Zito suggested studying children who were medicated for 5 years. Children diagnosed with disorders like bipolar disorder may be medicated continuously for many years. Dr. Robb said that children's medications change frequently. For example, a child with bipolar disorder may change medications two or three times in a year.

Dr. Zito said that an epidemiological approach could look for signals in retrospective data sets by examining a longitudinal cohort of children who were continuously covered by an insurance system for 5 years. Then subsequent studies could examine these signals.

Dr. Murphy agreed with this approach and said that FDA could not require a sponsor to conduct a prospective trial for 5 years. Dr. Robb noted that in rare instances the FDA does ask for long-term follow-up to examine specific endpoints.

Dr. Zito suggested that level 1 studies could examine a specific cohort across several specialized data sets to detect signals. Level 2 prospective studies could be traditional, small clinical studies recruited through academic centers. To make the sample representative of community treatment, studies could work with Kaiser or other entities with clinical health systems to add a prospective approach to collect information lacking in the retrospective data. This would allow the study to correct for biases in the retrospective data.

Dr. Poth said that endocrinologists do not know why patients under the age of 24 have an eight- or nine-fold higher rate of complications compared to older patients. She noted that patients taking antipsychotic drugs may gain weight and get type 2 diabetes with diabetic ketoacidosis, but when they stop taking the drugs and lose weight, the diabetes does not go away. This suggests that there is something else going on. This complication is more common in younger children. She suggested comparing children who develop diabetes with comparable children who do not develop diabetes to identify risk factors.

Dr. Taylor-Zapata said one of the major issues raised during the previous call was how to determine risk factors. The group also discussed the differences among drugs and among children. Some side effects are related to age, race, and gender. Some side effects are extrapyramidal rather than endocrine related or metabolic. Dr. Poth said she had not seen data on these types of side effects or on correlations between specific side effects. Dr. Robb said that risk factors for extrapyramidal symptoms include prior history and being young, male, and African American. She added that a study of aripiprozole found large differences in side effects in different racial groups.

Dr. Poth said that blood levels of drug might not correlate with dose. She noted that predisposing factors for metabolic syndrome were African American race, young age, obesity, and family history. Dr. Robb added that Native Americans and Hispanics also had a higher risk of developing diabetes with obesity.

It was noted that electronic health records could be an important source of data.

Dr. Crentsil asked whether systematic reviews or analyses would be useful. Dr. Poth said she did not think much data were available. Dr. Robb said a meta-analysis of FDA data could be helpful. She noted that a meeting about antipsychotics was being held the week of June 1. Dr. Poth asked whether the FDA data were available to the public. Dr. Cope said researchers could petition FDA for the data.

Dr. Zito said that a meta-analysis of short-term trial data would not be generalizable to children receiving continuous, long-term exposure. Duration of exposure is a critical issue in answering safety questions.

Dr. Murphy said that she and Dr. Cope could find out how many children have completed controlled prospective trials. Pediatric trials tend to be smaller than adult trials. Meta-analyses can be helpful in providing directions for research, but they cannot provide certainty. Dr. Cope said that drug trials focus on known adult AEs and may not pick up adolescent AEs. She noted that children tend to drop out of studies, possibly due to AEs.

Dr. Crentsil said that antipsychotic drugs are studied in the treatment of schizophrenia or bipolar disorder, but these drugs are used in the community to manage aggression and behavioral dyscontrol. There is a mismatch between community use and studies conducted for regulatory purposes. It is difficult to study this issue, because the diagnoses recorded may be diagnoses of convenience. He was asked whether aggression was not comorbid with diagnoses of oppositional defiant disorder or conduct disorder (CD). He responded that some might call this condition bipolar disorder not otherwise specified, but it is more like CD or severe attention deficit disorder (ADD). Dr. Crentsil described studies of the use of antipsychotics with stimulants for children with severe ADD and aggression. The studies are just starting, and data will not be available for a number of years.

Dr. Taylor-Zapata said that during the last call, the group raised the following issues:
- Comorbidity and concomitant medications
- A dream study of registration trials
- Advantages of electronic medical records
- Pulling signals from data sets.

Dr. Taylor-Zapata asked whether the group would like to discuss any additional issues. Dr. Paule asked whether there had been interest in pursuing these issues in animal models. Dr. Taylor-Zapata said the group had not discussed it, but it could be included in the list of recommendations. Dr. Paule said there were decent infant animal models that could be used to look for toxicity signals and AEs. Nonhuman primates vary significantly in their sensitivity to stimulants from infancy to adulthood.

Dr. Taylor-Zapata said that participants should have received an invitation to the 2009 BPCA annual scientific prioritization meeting, which will be held November 3–4 in Bethesda, MD.

Action Items:
- Participants will receive a survey and will vote on priority areas for study. The priority areas should be determined by July.
- A member of the group will need to volunteer to present the recommendations at the 2009 meeting.
- Dr. Manderscheid will send the Healthy People 2020 report to the group.
- Dr. Robb will send review articles on endocrine effects of antipsychotics to the group.
- Circle will prepare and distribute a draft of the conference call summary.

Addendum: Comment from Dr. Poth:
- There is a paucity of studies in children that document the mechanism or the time course of glucose intolerance and diabetes, in terms of whether it is insulinopenic diabetes, pure insulin

resistance, or a combination. There are also no studies that demonstrate the neuroendocrine or orexogenic hormones involved in the rapid weight gain seen with these drugs.